**UNITED STATES DISTRICT COURT**
**DISTRICT OF NEW JERSEY**

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| **ADAPT PHARMA OPERATIONS LIMITED, ADAPT PHARMA INC., ADAPT PHARMA LIMITED, and OPIANT PHARMACEUTICALS, INC.,**<br><br>**Plaintiffs,**<br><br>**v.**<br><br>**TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICALS INDUSTRIES LTD.,**<br><br>**Defendants.** | **Civil Action No. 16-7721 (BRM)(JAD) (Consolidated)**<br><br>**SUBJECT TO PROTECTIVE ORDER – CONTAINS CONFIDENTIAL AND OUTSIDE ATTORNEYS EYES ONLY INFORMATION** |

# PLAINTIFFS' TRIAL BRIEF

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## INTRODUCTION

This case is about NARCAN® Nasal Spray, the first and only FDA-approved, commercially available intranasal spray containing naloxone. Naloxone treats overdoses of opioids, a class of drugs that includes both prescription painkillers like oxycodone and illegal drugs like heroin. The misuse of opioids is a national epidemic, and NARCAN® Nasal Spray saves lives by making it possible for medically untrained individuals, such as police officers, and friends and family of opioid users, to administer naloxone and rescue overdose victims. NARCAN® Nasal Spray has been a runaway success. Priced affordably to ensure public access, it has grown since its approval in November 2015 to command more than 90% of the retail naloxone market. Thanks to Plaintiffs' invention, tens of thousands of people across the country now have access to a life-saving treatment for opioid overdose at their fingertips, ready to use in the event a friend or loved one overdoses. As the *Wall Street Journal* recently reported: "When asked why [overdose] fatalities in the Pittsburgh area fell 41% to 432 last year . . . Allegheny County Chief Medical Examiner Karl Williams said: 'In a word, Narcan.'" Ex. XX at 2.

The invention that made NARCAN® Nasal Spray possible is reflected in several patents issued by the U.S. Patent & Trademark Office and asserted here against Defendants (collectively, "Teva"). The patent claims are generally directed to pharmaceutical formulations for intranasal administration of naloxone, single-use devices for delivering those formulations, and methods of treating opioid overdose using those formulations and devices. [redacted] Teva does not dispute that it infringes Plaintiffs' patents, [redacted] Teva also does not dispute that Plaintiffs' invention was novel. No one had made it, used it, or described it before Plaintiffs. Rather, Teva argues that even though no

one actually made the claimed invention before Plaintiffs, the patent claims are supposedly invalid because the invention was obvious from convoluted combinations of prior art references.

Teva is in no position to make this claim. Plaintiffs' patents disclose and claim doses of 4 mg of naloxone. [redacted]

Teva's surprise was understandable. Plaintiffs' claimed dose of 4 mg of naloxone was unprecedented. Multiple prior art studies, in which naloxone was administered intranasally using improvised devices, found a dose of 2 mg or less to be safe and effective. Meanwhile, the art taught that giving too much naloxone risked dangerous, even fatal, withdrawal effects, a problem highlighted in countless prior art publications. Thus, the then-conventional thinking was to strike a balance: use the lowest generally effective dose of naloxone and provide an additional dose only if needed. Every single piece of prior art Teva relies on concludes that the appropriate dose for an intranasal naloxone product would be 2 mg *or less*. Not one recommends a higher dose or says that anything is wrong with the 2 mg dose that was being administered using an improvised device.

Teva attempts to get around this fatal flaw in its case by fabricating a problem not identified anywhere in the literature. Using improper hindsight, Teva co-opts the inventors' own unique thinking and argues that the hypothetical person of ordinary skill in the art ("POSA") would have wanted to avoid administering an additional dose of naloxone—that is, to avoid a situation where, having given a dose of naloxone and needing to give more naloxone to achieve a full response, users administer a second dose. If this were anything but improper hindsight, it would be reflected in at least one of Teva's prior-art references. It isn't. No reference identifies additional doses as a problem, much less recommends an intranasal dose higher than 2 mg. Instead, the references repeatedly caution *against* higher doses because of concerns about withdrawal.

Teva is left to argue that the 4 mg dose can be found in what it characterizes as "ranges" of doses in the prior art. But in order to meet its clear and convincing evidentiary burden of proving obviousness, Teva has to prove much more than that the number 4 can be found within a range somewhere. Teva must prove that the POSA would have been motivated to use that specific dose. This Teva cannot do, because its arguments run afoul of the references' express teachings, each of which expressly prefer much lower doses, *i.e.*, 2 mg or less. Plaintiffs' approach to dosing was unprecedented, and Teva's arguments amount to nothing more than improper use of hindsight.

Teva's remaining obviousness arguments fare no better. For example, Teva argues that the use of benzalkonium chloride ("BZK") as a preservative would have been obvious because it is well-known. But the closest prior art reference, and the *only* one to disclose stability testing of naloxone formulations with BZK, expressly instructs *not* to use BZK because it degrades the naloxone and therefore creates an unstable product. Teva also fails to explain why the POSA would have been motivated to choose a single-spray dosing regimen, when the prior-art clinical practice consistently was to administer naloxone to a patient through two sprays, one to each nostril. Teva cannot overcome these significant problems with the individual claim limitations, much less can it

demonstrate the obviousness of combining *all* of the claimed features. As the Supreme Court has emphasized, it is not enough to find the various limitations somewhere in the art; it is incumbent on Teva to prove that the POSA would have combined them in the claimed fashion. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

Beyond the art itself, there is abundant objective evidence that the claimed invention was not obvious. [redacted]

Teva's remaining arguments that certain claims are invalid under 35 U.S.C. § 112 are no more meritorious. Plaintiffs are entitled to judgment in this case.

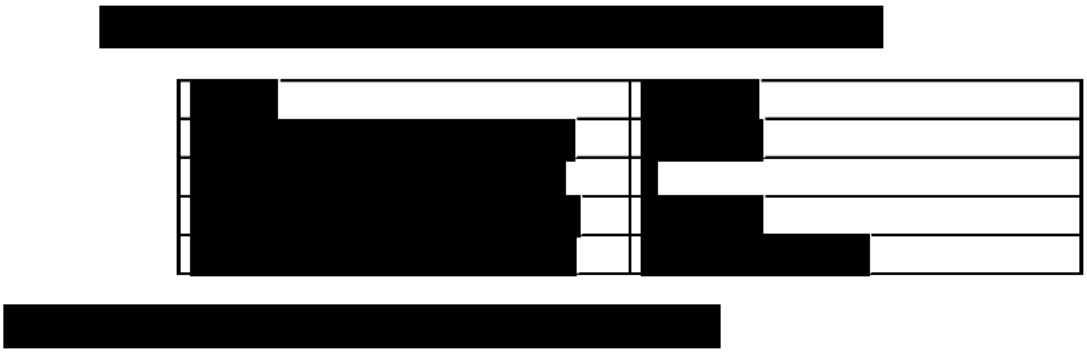
## I. Background

### A. Naloxone Use in the Community Context

Naloxone is an "opioid antagonist," a chemical that reverses the effects of opioid drugs. A patient who overdoses on opioids can lose consciousness and experience respiratory depression (*i.e.*, stop breathing). Administration of naloxone counteracts these potentially fatal effects. First introduced in 1971, naloxone has historically been administered by IV or intramuscular injection by trained medical providers. With the progression of the opioid crisis, however, more opioid overdoses occur in so-called "community" settings where trained medical providers are not present.

The administration of naloxone through IV or intramuscular injection poses practical challenges for people without medical training. Even first responders such as police officers, firefighters, and many basic-level EMTs are not authorized to administer injections. For years before the approval and launch of NARCAN® Nasal Spray, the primary option for individuals with limited training was to combine a naloxone injection product with a disposable Mucosal Atomization Device ("MAD") to create an improvised nasal delivery system. This system required a tricky eight-step assembly, which was not ideal for lay people acting under pressure. And because it used naloxone formulations intended for injection, the system delivered a volume of liquid far too large for the nose in a formulation not designed for nasal administration.

**B. The Asserted Patent Claims and Infringement**



The asserted claims generally relate to pharmaceutical formulations, methods of treating opioid overdose, and devices. Generally, the formulations comprise about 4 mg naloxone hydrochloride, between about 0.005 mg and about 0.015 mg of BZK, between about 0.1 mg and about 0.5 mg of disodium edetate ("EDTA"), between about 0.2 mg and about 1.2 mg of sodium chloride ("NaCl"), and an amount of acid sufficient to achieve a pH of 3.5–5.5, in about 100 μL (microliters) of solution. The claims generally provide that the formulations are delivered into one nostril of the patient by using a single-use, pre-primed device adapted for nasal delivery.

The priority date applied by all parties is March 2015. The parties also generally agree that the POSA would have had expertise in developing nasal pharmaceutical formulations and knowledge of and clinical experience with administration of opioid antagonists to treat overdoses.

## II. The Asserted Claims Are Not Obvious.

Not a single prior art reference disclosed any of the asserted claims. They cannot even be arrived at by combining two or more references. Rather, Teva purports to identify the claimed combination of dose, formulation, device, and method of administration in two separate combinations of references, each combination cobbling together pieces from three or four different references—totaling *seven* different references. To prevail, Teva must establish—by clear and convincing evidence—that the POSA would have had reason to combine these references in a manner that would have led to the claimed combination, and with a reasonable expectation of success. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). Teva cannot come close to meeting this exacting burden.

[redacted]. Instead, Teva cherry-picks from other references. Its arguments are not only inconsistent with the art as a whole, but with the teachings of its own preferred references, and even with its own other arguments. For example, Teva argues that the POSA would have increased the dose from 2 mg, apparently out of a concern (found nowhere in the art) that the POSA would have wanted to avoid administering an additional dose to patients who did not respond adequately to the first dose. Yet, simultaneously, Teva argues that there was no need for a different or better naloxone regimen than the 2 mg and lower products already available. Teva's own experts characterize prior-art 2 mg regimens using the MAD as "successful" and "the gold standard." Teva even suggests that based on all we know today, a 4 mg dose of naloxone has no greater therapeutic effect than a 2 mg dose—a notion that is inconsistent

with the impressive pharmacokinetic data for Plaintiffs' 4 mg product. But if Teva were correct and "no 'problem' was perceived" by the POSA with a 2 mg dose, the POSA would have had no reason to select a higher dose. *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349–50 (Fed. Cir. 2000). The fact that Teva's arguments are nowhere near consistent with each other shows them to be litigation-driven hindsight.

And that is only dose. Teva cannot show that the POSA would have administered that dose all at once, to one nostril, or in a single-use device. Teva cannot show that the POSA would have included BZK in the formulation, much less in combination with EDTA. And Teva cannot show that the POSA would have had a reasonable expectation of success. For these reasons and those described further below, Teva certainly cannot show that the entire claimed combination of dose, formulation, device, and method of administration would have been obvious.

### A. The POSA Would Not Have Chosen the Claimed 4 mg Dose and Method of Administration.

1. The administration of a concentrated 4 mg dose of naloxone was unprecedented, despite decades of experience administering naloxone to overdose victims. There was no recognized need to increase the widely accepted intranasal starting dose, and there were well-recognized reasons to avoid doing so. In fact, Teva's own experts affirmatively opine that by March 2015, the POSA understood that doses of 2 mg (or less) of intranasal naloxone were known to be an effective way of reversing opioid overdoses.

That is also what the art teaches. The prior art reporting on clinical administration of intranasal naloxone used a dose between 0.4 mg to 2 mg intranasal naloxone:

| Reference | Dose | Concentration | # Nostrils | Effective? |
|---|---|---|---|---|
| Loimer 1992 (Ex. D) | 1 mg | 2.5 mg/mL | Not stated | N/A |
| Loimer 1994 (Ex. E) | 1 mg | 2.5 mg/mL | Not stated | N/A |
| Kelly 2002 (Ex. H) | 0.8 mg–2 mg | Not stated | Not stated | Yes |
| Barton 2002 (Ex. G) | 2 mg | 1 mg/mL | 2 | Yes |
| Barton 2005 (Ex. J) | 2 mg | 1 mg/mL | 2 | Yes |

| Reference | Dose | Concentration | # Nostrils | Effective? |
|---|---|---|---|---|
| Kelly 2005 (Ex. K) | 2 mg | 0.4 mg/mL | 2 | Yes |
| Doe-Simkins 2009 (Ex. P) | 2 mg | 1 mg/mL | 2 | Yes |
| Kerr 2009 (Ex. Q) | 2 mg | 2 mg/mL | 2 | Yes |
| Robertson 2009 (Ex. R) | 2 mg | 1 mg/mL | 2 | Yes |
| Merlin 2010 (Ex. T) | 2 mg | 1 mg/mL | 2 | Yes |
| Walley 2013 (Ex. CC) | 2 mg | 1 mg/mL | 2 | Yes |
| Sabzghabaee 2014 (Ex. EE) | 0.4 mg | 0.2 mg/mL | 2 | Yes |

All of the references reporting on overdose treatment found a dose of 2 mg or less to be effective, and not one suggested that such an intranasal dose was ineffective or insufficient.

Although he now testifies that a 4 mg dose would have been obvious, Teva's expert, Dr. Mark Merlin, published a paper in 2010 comparing patients who had received a mean 1.95 mg dose of naloxone intranasally via a MAD, and patients who had received a mean dose of 1.71 mg by IV. Merlin 2010 (Ex. T) at 300. Dr. Merlin concluded that "[i]ntranasal naloxone is statistically as effective as IV naloxone at reversing the effects of opioid overdose." *Id.* at 296. Far from recommending a higher dose, Dr. Merlin stated that it would be "difficult to determine whether our primary outcome measures would have changed if 2 mg per nostril was used and if this change would be dose-dependent." *Id.* at 302.

2. Although the prior art is devoid of any teaching advocating an intranasal naloxone dose higher than 2 mg, there is a wealth of evidence *against* increasing the dose. The POSA would have understood that the administration of naloxone to opioid users could trigger harmful (and potentially life-threatening) consequences for the patient and bystanders, a problem that increases with increasing naloxone dose. Dozens of references (including Wyse, the closest prior art) warned against increasing the naloxone dose because of these serious risks.

The POSA would have known that naloxone administration can precipitate withdrawal symptoms ranging from agitation or irritability, anxiety, body aches, nausea, or vomiting, to more severe reactions including acute respiratory distress syndrome, hypertensive emergency, ventricular

tachycardia and fibrillation, and even sudden death—at doses as low as 0.04 mg to 0.4 mg intravenously. Schwartz 1987 (Ex. B) at 1295. Administration of too much naloxone can also lead patients to refuse medical care, and even engage in "lethal" drug-seeking behavior in order to cope with withdrawal symptoms. Zuckerman 2014 (Ex. GG) at 552. The prior art also reports numerous incidents in which patient agitation and violence from the administration of naloxone created a risk of harm to bystanders, to the point that the patient had to be physically subdued by police. *E.g.* Gaddis 1992 (Ex. C) at 196. One reference observed that 13% of patients treated with naloxone exhibited agitation and combativeness, Belz 2006 (Ex. M) at 470, so much so that the prior art recommended that "adequate preparation . . . in the form of restraints is needed." van Dorp 2007 (Ex. O) at 128.

For these reasons, the typical method of administering naloxone, even by trained people, has always been slowly to increase the dose over time "according to the patient's needs," and to administer "*as low a dose as possible*" initially, to avoid withdrawal. Buajordet 2004 (Ex. I) at 21; Pallasch 1981 (Ex. A) at 603 (emphasis added). Although the FDA-approved label for IV and intramuscular naloxone permits giving a *total* dose of up to 10 mg, it expressly caps the *initial* dose at no more than 2 mg, and the standard of care is to start with a dose of 0.4 mg and slowly "titrate" up to effect. This is precisely to avoid inducing withdrawal unnecessarily. Teva dismisses these concerns, pointing to evidence that the administration of naloxone to *healthy* people who have not been taking opioids is safe at high doses. But, as Dr. Merlin acknowledges, this is entirely beside the point, as withdrawal is a concern for patients who *have* been taking opioids—the very patients who need naloxone to treat an overdose. Teva also asserts, without literature support, that the POSA would for some reason consider withdrawal to be a non-issue for intranasal naloxone dosing, but there is no basis for this view, particularly in light of the fact that there was no prior-art use of an intranasal formulation of a concentrated dose above 2 mg. Teva's assertions that the POSA would

not have been concerned about the dangers of too high a dose are not credible. The POSA would not have increased the dose above 2 mg.

3. Without credible support for its theory that the POSA would have selected a 4 mg dose, Teva is forced to rely on references that affirmatively recommend a 2 mg or lower dose, *not* a 4 mg dose. Teva focuses on particular statements in the references that it deems helpful, while ignoring the references' articulation of what their authors preferred or concluded. Unsurprisingly, this hindsight-driven cherry-picking of only portions of a prior art reference directly contravenes obviousness precedent. *Polaris Indus., Inc. v. Arctic Cat, Inc.,* 882 F.3d 1056, 1069 (Fed. Cir. 2018). Teva's own references and the closest prior art undermine its case.

***Wyse:*** The Wyse patent (Ex. OO) is prior art under 35 U.S.C. § 102(a)(2) and is the undisputed closest prior art in this case. [redacted] It is the latest-in-time reference and reflects the extensive work of AntiOp in developing an intranasal product for an FDA submission. AntiOp was led by Dr. Daniel Wermeling, whom Teva's experts described as "a leading expert" on intranasal drug administration with a focus on naloxone "for at least the past decade." [redacted]

Wyse expresses concern, which the POSA would have shared, about the "dangerous" effects of naloxone's "rapid[] revers[al] [of] the effects of the opioid," and expressly seeks to avoid triggering such withdrawal effects. Wyse (Ex. OO) at 2:8–22. Wyse then identifies "a need for effective formulations and methods of providing such compositions to an individual … that can be quickly and easily used, but which *minimize sudden and severe side effects of rapid reversal of opioid overdose*."

*Id.* at 3:3–8. Reporting on data obtained in a pilot study testing 1 mg and 2 mg intranasal naloxone formulations, Wyse explains that the objective was to *avoid* replicating the spike in naloxone plasma concentration that results from IV administration because slower increase in naloxone blood levels would likely decrease withdrawal effects. *Id.* at 16:33–40.

Wyse concludes that the appropriate intranasal naloxone dose is 2 mg, administered as 1 mg per nostril. Wyse even lowered the concentration of his formulations—having already started below Plaintiffs' claimed 4 mg per 100 μL concentration—which allowed him to divide the dose between two nostrils. *See id.* at Examples 4–7 (formulation screening using 20 mg/mL), Examples 1–3 (exemplary compositions and clinical studies using 10 mg/mL). Wyse's dose and decision to administer it via two nostrils instead of one is consistent with the rest of the art and inconsistent with Teva's position that Plaintiffs' 4 mg-in-one-nostril claims are obvious.

Wyse also teaches the administration of a 2 mg dose, waiting 5 minutes and, if needed, administering a 2 mg backup dose "if the initial dose is insufficient," in order to "mirror[] clinical practice with naloxone injection." *Id.* at 24:1–6. Wyse affirmatively did *not* propose a 4 mg starting dose. Instead, Wyse is consistent with the rest of art, teaching that the appropriate practice is to administer a 2 mg initial dose and only administer a second dose *if needed*, just as the POSA would have believed. In developing an intranasal product, the POSA would have looked to Wyse's examples and the clinical prior art, both of which taught that a 2 mg dose or less would be effective, with the option of administering an additional dose if needed.

***Strang:*** Another of Teva's lead references, the Strang publication (Ex. AA), undisputedly recommended an initial intranasal dose of between 1.3 and 1.6 mg naloxone, claimed only those doses, and did extensive modeling only of doses between 1.2 and 1.6 mg. Although Strang reported tests in which a total of 8 mg and 16 mg intranasal doses of naloxone were administered via two nostrils to healthy volunteers, he did not recommend either dose (or for that matter 4 mg). Rather,

Strang was using healthy volunteers to measure the extent and speed with which intranasal naloxone gets into the bloodstream—*i.e.*, the pharmacokinetics—in order to find an intranasal dose to match the "typical starting point" of 0.4 mg intravenous naloxone:

> Based on the AUC-values for 1 mg IV naloxone, 8 mg IN [intranasal] naloxone and 16 mg IN [intranasal] of example 1, it can be estimated that the range of dose-proportionality to 1 mg IV is in the range of 3 mg to 4 mg for IN [intranasal] naloxone. For 0.4 mg IV naloxone, this results in typical starting amounts for naloxone administered intranasally ranging from 1.2 mg to 1.6 mg.

Strang at 48:15–20. Teva tries to turn the first sentence into a teaching toward a 4 mg dose, completely ignoring the conclusion. Strang merely used the "3 mg to 4 mg" estimate in a calculation of the appropriate—and lower—intranasal dose of 1.2 mg to 1.6 mg.

Teva is left relying on other parts of Strang's specification—which includes a laundry list of embodiments, amounts, concentrations, and dosing regimens. Teva suggests that Strang discloses a range of doses from 0.5 to 20 mg, from which the selection of 4 mg would presumptively have been obvious because merely optimizing a value from within a prior-art range typically does not confer patentability. *E.g.*, *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1304–05 (Fed. Cir. 2015). But for a value within a disclosed range to be obvious on this theory, the POSA must have a reason to "find an optimum value" within the range. *See, e.g.*, *Genetics Institute, LLC v. Novartis Vaccines & Diags., Inc.*, 655 F.3d 1291, 1306 (Fed. Cir. 2011). That is not the case here, as the POSA would not have looked to Strang's broad disclosures in the first place. The "range" case law Teva invokes also is inapplicable if "the prior art taught away from the claimed range"—as the prior art addressing withdrawal symptoms does here—or where, as here, the range is "very broad." *E.I. DuPont de Nemours & Co. v. Synvina CV*, 904 F.3d 996, 1006 (Fed. Cir. 2018). Strang, in any event, does not simply disclose a numerical range; Strang contemplates a vast set of permutations of initial doses, total doses administered any number of minutes apart over time, doses administered in different concentrations, and doses administered via one or two nostrils. Teva cannot simply cherry-pick a

single initial dose of 4 mg administered to a single nostril, without any explanation for why the POSA would have made this particular selection despite Strang's clear recommendation for a dose of 1.3 to 1.6 mg or his own use of two nostrils. The POSA would not ignore the clear recommendation of the reference, the consistent clear teachings and preferences of every *other* prior art reference, and the extensive literature on avoiding the inducement of withdrawal, and nonetheless pick a 4 mg dose.

***Davies:*** Teva also relies on Davies (Ex. F), a device patent issued on October 26, 2000. Davies does not disclose any clinical data, pharmacokinetic testing, formulation development, or stability testing, and it pre-dates all the published clinical reports on treating overdose patients with intranasal naloxone. It is inconceivable that the POSA would have given Davies any weight 15 years after its publication. Even Teva's own expert readily conceded that one would look to references with actual clinical data instead. But if the POSA were to have taken anything from Davies, it would have been that the "especially" preferred dosing range for naloxone or naltrexone or combinations of the two is "0.4 to 1.6 mg," Davies at 3:2–3, as confirmed in Davies' Example 1, which teaches a dose of 400 μg (0.4 mg), *id.* at 4:5. As in Strang, the POSA would have had no reason to look to any supposed broader "ranges" in Davies, which like Strang contemplates vast permutations of dosing regimens, nor is the case law regarding optimizing ranges relevant in light of Davies' teachings and the prior art. Teva's suggestion that Davies would have led the POSA to a dose of 4 mg, to a single nostril of a patient, using a single-use device, is simply wrong.

***Kerr 2009:*** In addition, Teva relies on Kerr 2009 (Ex. Q), which compared the effectiveness and safety of intranasal and intramuscular naloxone. Kerr 2009's express conclusion is that "administration of naloxone via the i.n. route" to overdose victims "is a safe and effective treatment option." Kerr 2009 at 2072. Kerr 2009 compared the effectiveness of 2 mg intranasal naloxone (split between two nostrils, at a volume of 0.5 mL per nostril) to intramuscular naloxone. *Id.* at

2068. Kerr 2009 concluded that the time to patient response was almost identical for the intranasal and intramuscular groups (8.0 minutes and 7.9 minutes, respectively), and that there was no statistically significant difference in the percentage of patients who exhibited an adequate response within 10 minutes. *Id.* at 2070.

Despite this clear teaching that a 2 mg dose of intranasal naloxone was safe and effective, Teva tries to interpret Kerr 2009 as a teaching of a *higher* dose—a dose Kerr 2009 never mentioned—to avoid giving a patient a second dose of naloxone if, after some period of time, the patient does not respond adequately to the first one. Teva bases this on Kerr 2009's observation that among the patients who did not respond within 10 minutes, more of the intranasal patients received an additional dose of naloxone. Teva ignores the express teachings of the reference and then assumes a different conclusion. Kerr 2009 did not identify these additional doses as a concern or a reason to change the starting dose. On the contrary, Kerr 2009 attributed the difference to the reality that the study was not blinded, that "[a]dministration of rescue naloxone . . . was a subjective decision made by paramedics at the scene," and that given their unfamiliarity with the intranasal route, they "might have administered secondary naloxone to patients who received the [intranasal] allocation due to apprehension about the effectiveness of the [intranasal] treatment option." *Id.* at 2072. Critically, Teva's expert, Dr. Merlin, agrees that the POSA would not have made anything out of Kerr 2009's comparative re-dosing data. To the contrary, according to Dr. Merlin, it would be a "terrible premise" to say that there was a meaningful difference in those numbers.

Moreover, Dr. Merlin conceded that Teva cannot point to *any* prior art reference that identifies the possibility of needing to administer an additional dose as a problem to be solved, much less recommends increasing the 2 mg intranasal dose. Administering an additional dose was and is a common practice when naloxone is administered, and the POSA would have understood that it was well within the ability of laypersons in the community, as Dr. Merlin admits. As Plaintiffs' clinical

expert, Dr. Ken Williams, will testify, it simply requires someone to administer a dose, wait a few minutes, and then administer another dose if the patient does not improve. Wyse, for example, discloses exactly this procedure, and it also is suggested by the labels of both FDA-approved community-use naloxone products, NARCAN® Nasal Spray and EVZIO®, an intramuscular naloxone autoinjector. Clinical studies in real-world settings confirm that lay persons are perfectly capable of administering an additional naloxone dose if needed. *E.g.*, Walley 2013 (Ex. CC) at 9 tbl.3. And the POSA would have selected this approach over raising the naloxone dose for all patients and thus increasing the risk of withdrawal, as discussed above in Section II.A.2. In any event, if the POSA had nonetheless been motivated to eliminate additional doses, then there is no reason to believe the POSA would have arrived at a 4 mg intranasal dose rather than a materially higher one, in light of the prior art's report of cases requiring repeat dosing up to 10 mg IV naloxone.

4. Given the wealth of prior art that undermines its case, Teva argues that the so-called "fentanyl crisis" would have motivated the POSA to reconsider that art. There is simply no basis for this assertion, either as a matter of timing or substance. The increase in fentanyl distribution that is a recognized problem today was not yet a recognized trend in 2015, and would not have motivated the POSA. For example, the most recent DEA National Drug Threat Assessment ("NDTA") as of the priority date only noted fentanyl in the context of being mistaken with or tainting heroin. *See* Ex. FF at 1, 15. And in 2015, the NDTA concluded that fentanyl was "unlikely to assume a significant portion of the opioid market." Ex. HH at 43. Fentanyl was not even mentioned on the CDC's opioid epidemic webpage in 2015. *See* Ex. PP.

In any event, even if the POSA had recognized a growing "fentanyl crisis," that does not mean the POSA would have wanted to give a higher initial dose of naloxone (or would have been any less worried about the risks of doing so), and no prior art reference suggests that the POSA

would have done so (either to opioid users generally or fentanyl users specifically). The presence of more potent opioids does not mean that the effective opioid doses consumed by the overdose victims are higher. The POSA would have expected that overdose victims are likely to consume a much smaller amount of fentanyl, and would have understood that a victim may suffer from less severe overdose if they consume a small amount of fentanyl than if they consume a large amount of natural opioids.

[redacted] The prior art taught that, because the nose cannot retain volumes greater than a few hundred microliters per nostril, the percent absorption of intranasal administration of 2 mg of naloxone in 2 mL of fluid was quite low. The percent absorption of 4 mg naloxone in 4 mL of fluid—the equivalent of approximately 8 times the amount the nose can hold—would be even lower. Notably, Dr. Merlin was entirely unable to testify that the pharmacokinetics of his alleged practice exceeded those of the somewhat more concentrated 2 mg dose described in Wyse, much came anywhere close to corresponding to the highly concentrated 4 mg dose in 100 μL—one-tenth of one mL, or forty times less fluid—that the patents-in-suit claim.

5. Finally, the hindsight nature of Teva's arguments about naloxone dosing are only further illustrated by an additional hole in its case. A key limitation in the asserted claims is the requirement of a single-actuation device that delivers the dose as a single spray to a single nostril.

That approach is directly contrary to how the clinical studies and the key references—including Strang, Wyse, and Kerr 2009—administered naloxone: dividing the amount in half to be sprayed into both nostrils. Other than unsupported hand-waving about simplicity, Teva does not identify a reason for the POSA to have deviated from this approach, which, among other things, accounts for the possibility that one of the patient's nostrils is stuffed up or damaged.

In fact, nothing about the inventors' approach to dosing was obvious. Although Teva will no doubt trumpet that the Aptar device that NARCAN® Nasal Spray uses was known in the art, Teva concedes that it was but one of many possible devices available to the POSA. For example, Djupesland, one of Teva's references, identifies a total of 22 categories of nasal delivery devices from which a device could be selected to achieve a desired dosing regimen. Djupesland (Ex. BB) at 47 tbl.1. And in the context of naloxone, "[t]his 'divided' way of administration"—dosing across two nostrils—plainly "[wa]s preferred." Strang (Ex. AA) at 19:27–20:2; *see also* Wyse (Ex. OO) at 10:13–24, 11:10–19, 11:35–40. Thus, while Wyse selected the Aptar UnitDose Device, Wyse's dosing regimen still did not parallel the claimed regimen because Wyse elected to administer one half-dose to each nostril by using two UnitDose devices. Wyse at 15:36–49.

**B. The POSA Would Not Have Developed a Formulation with BZK and EDTA.**

Teva's inability to show obviousness of a concentrated 4 mg-in-one-nostril dose of naloxone is only one fatal flaw in its case. The prior art also expressly teaches away from using BZK and from using the combination of BZK and EDTA, as the claims require.

1. Teva's formulation expert has correctly observed that the Wyse patent is the prior art reference that provides the most useful information about how to formulate naloxone for intranasal use. But Wyse undermines Teva's case. Wyse teaches that while certain other preservatives "were acceptable," BZK—the preservative in Plaintiffs' claimed invention—"was not, due to increased observed degradation." Wyse (Ex. OO) at 27:43-44. Because chemical instability would

undisputedly pose a serious problem for a commercial naloxone formulation, Wyse would have led the POSA away from the use of BZK (particularly in combination with EDTA, another claimed excipient) and thus away from the claimed invention.

[redacted]. But Wyse is the only reference to disclose stability testing of naloxone formulations containing BZK. Not only did Wyse conclude that BZK was not acceptable in naloxone formulations, but that conclusion was based on the *only* stability testing reported in any prior-art reference in the case about the effects of BZK on naloxone. Wyse at 26:35–27:16 (Table 13), 27:29–32. And Wyse put his money where his mouth was: following the preliminary formulation screening study that revealed the problems that BZK caused, Wyse conducted an additional screening study analyzing four excipient combinations "under stress conditions." *Id.* at 28:41–44. Ten excipients were used, *but not BZK*, which he had abandoned. *Id.* at 27:46–50. Wyse then pursued a formulation ("Formulation 7M") with benzyl alcohol, an alternative preservative, instead of BZK in further stability studies and his final formulation. *Id.* at 28:52–29:27. In the face of this evidence, the POSA would have eschewed the use of BZK.

2. Teva's first response to this evidence is to ignore it. Teva looks to three other references that supposedly teach BZK: Davies (Ex. F), Kulkarni (Ex. W), and the [redacted] (Ex. L). Davies—the only one of these that is a prior-art publication about naloxone—is a fifteen-year old patent. According to Teva, the POSA would have found it meaningful that Davies contained one naloxone formulation containing BZK, albeit not in the claimed concentration and without any EDTA. But given that Davies did not have the benefit of Wyse's stability data and that Davies himself did not generate or disclose any stability data, the POSA, at the time of the invention and

with the benefit of Wyse, would not somehow have inferred from this that BZK and naloxone were compatible.

Kulkarni is a general publication about intranasal formulations that does not mention naloxone, much less provide information about its stability. It would not override Wyse's teachings that were based on stability testing of naloxone formulations. *See Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1376–77 (Fed. Cir. 2019) (affirming decision that "specific, directly applicable teachings" should be applied in preference to "tangential, general statements"); *see also In re Lunsford*, 357 F.2d 385, 391 (C.C.P.A. 1966) ("It is not believed that [the POSA] . . . would disbelieve specific teachings and rely only on less helpful general statements."). Presumably, Teva identified Kulkarni because it discusses BZK, but that is an impermissible application of hindsight to the question of how the POSA would have gone about designing a formulation.

[redacted]

3. Recognizing that it must somehow grapple with Wyse, Teva attempts to undermine it, but its responses are not credible. First, Teva observes that in reporting on the formulations that had stability problems, Wyse omitted one of the formulations that contained BZK. That is, Wyse

tested formulations numbered 7, 9, 12, 14, and 14A with BZK, but then stated that there was an "additional degradant in formulations 7, 9, 14, and 14A." Wyse (Ex. OOs) at 27:29-32. From this, Teva infers that Formulation 12 did not have a stability problem, and that the POSA would have concluded that BZK was acceptable. There are several problems with this theory. It contradicts Wyse's own express conclusions. It also ignores that Formulation 12—unlike three of the four that Wyse expressly disclosed to have a stability problem—did not contain EDTA. *See id.* at 26:35–27:17 (Table 13, formulations 7, 14, and 14A). And Wyse reported that every formulation tested that did contain both BZK and EDTA was unstable. If anything, the POSA would have concluded that if BZK was ever suitable for use with naloxone, it was in formulations that lack EDTA—a conclusion that would point away from the claims, which require EDTA.

[redacted]

Teva's second response to the Wyse data is to argue that the POSA would have inferred that the concentration of BZK in the Wyse formulations was too high. Kulkarni teaches that it is *not* too high, so Teva looks to *yet another* general-purpose reference, the Handbook of Pharmaceutical Excipients (Ex. S), that discusses BZK in contexts unrelated to naloxone. [redacted] Teva's theory that the POSA would have doggedly pursued a working BZK formulation makes no sense. For one thing, the POSA would have had no reason to believe that such a

formulation existed regardless of concentration; a destabilizing excipient would still have that effect at lower concentrations. [redacted]

4. In fact, instead of scrambling to try to make BZK work in the face of a manifest instability problem, the POSA would have just followed Wyse, which had already disclosed a highly stable formulation with benzyl alcohol as a preservative instead of BZK. Or the POSA would have decided just to omit a preservative, as such a preservative was not required. Preservatives are important in multi-use formulations, where after a container or device is opened for the first time, the sterile formulation may be contaminated by microbes, which can grow in the formulation. The devices applicable here—and that Teva claims would have been obvious—are used once. There also were strong reasons *not* to use a preservative. [redacted] The POSA would have known that some regulators would require "special justification" for preserved formulations due to potential toxicity concerns. Ex. N at 3. And the POSA would have known multiple preservative-free nasal formulations, including IMITREX®, ZOMIG®, and MIGRANAL® nasal sprays, that had been formulated consistently with this concern. Another option, moreover, would have been to create a solid product that did not have the stability problems of BZK and naloxone in a liquid formulation. Intranasal powders were a viable alternative. *See* Middleton 2011 (Ex. U) at 8. If the POSA had not wanted simply to follow Wyse, therefore, the POSA would have gone in a different direction, not continued to pursue a BZK formulation in the face of Wyse's contrary teachings.

**C. Teva Cannot Demonstrate Obviousness of the Claimed Combination.**

1. The non-obviousness of the claimed concentrated 4 mg dose, particularly in a single spray in a single nostril, is enough to defeat Teva's case. So is the non-obviousness of using BZK

and EDTA with naloxone. But even if Teva could find precedents in the literature for each of these individual claim elements—and it cannot—Teva erroneously ends the analysis there. Teva's analysis of obviousness contravenes the hornbook principle that there must be a "reason to combine the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418.

The first obviousness combination that Teva's experts have addressed—Strang in combination with Kulkarni and Djupesland—is illustrative. As discussed above, Teva cherry-picks parts of Strang in search of a teaching of the required 4 mg naloxone dose. But because Strang has essentially nothing to say about formulation excipients, Teva then turns to a general reference that has nothing to do with naloxone, Kulkarni, to identify the other formulation excipients and concentrations of those excipients, and a third reference, Djupesland, to identify the device. That is logical if one is looking *retrospectively* for precedents in the art for each claim limitation. But that is exactly the *opposite* of how an obviousness analysis is supposed to work, where the question is what the POSA would have been motivated to do in light of the prior art.

The problem is compounded, moreover, because Teva needs to prove not only a combination of particular excipients, but particular claimed *quantities* of those excipients. Teva attempts to solve this problem by identifying individual prior art disclosures of amounts of naloxone, amounts of BZK, amounts of EDTA, and so forth, often disclosed only as ranges that encompass the claimed values. That does not suffice. This is not a circumstance where the claimed combination of ingredients was known and Teva merely needs to show that a particular concentration of one ingredient is obvious; the whole formulation is novel. Teva therefore must supply "a motivation to select the claimed composition from the prior art ranges." *Allergan*, 796 F.3d at 1304–05 (Fed. Cir. 2015). Moreover, the various ingredients in pharmaceutical formulations all interact in "unpredictable" and "unexpected way[s]," undermining any argument that the POSA would have arrived at the claimed numerical values merely by starting with prior-art ranges and

somehow optimizing the formulation. *In re Applied Materials*, 692 F.3d 1289, 1298 (Fed. Cir. 2012).

2. Teva's assertion that it would have been obvious to select the claimed invention from all the myriad possible permutations of formulation, device, dose, dosing regimen, and other parameters is undermined further by the simple reality that numerous research groups—[redacted]—were working in the field, and none arrived at the claimed formulations.

*AntiOp:* [redacted]

***Mundipharma:*** Dr. Strang—another author of Teva's asserted prior art—collaborated with a company called Mundipharma to develop a single-spray nasal naloxone product with a 1.8 mg dose—less than the claimed invention. Ex. VV at 11. It arrived at a different combination of excipients: trisodium citrate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide, and purified water—unlike the invention, not BZK or EDTA. *Id.* And again, Mundipharma's product has not been approved for use in the United States.

***Amphastar:*** Amphastar Pharmaceuticals, the manufacturer of the naloxone syringe used in conjunction with the MAD, developed a nasal naloxone product with a 2 mg dose delivered in a 0.5 mL volume. *See* Ex. TT at 1–2. [redacted] Amphastar's product, like the others, has not been approved in the United States. *See* Ex. TT at 2.

***Teva:*** [redacted]

[redacted]

3. In contrast to everyone else in the field, the inventors of the patents-in-suit made different decisions about each of the relevant aspects of what became the patented product, for reasons that would not have motivated the POSA. [redacted]

[redacted]

Teva takes this story and tries to turn it against the patents, passing it off as reflective of the perspective of the POSA. But that is not how obviousness is supposed to be analyzed. Every inventor has an internal justification for his or her invention, but the law recognizes that it "is hindsight," and improper, to consider "the inventor's own path" when evaluating obviousness. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012); *see Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. Inc., USA*, 748 F.3d 1354, 1360 (Fed. Cir. 2014).

Teva even goes so far as to cite Plaintiffs' own documents, written from the inventors' perspective. Indeed, Teva's lead expert, Dr. Smyth, has paragraphs of his expert opinion that are supported exclusively by non-prior-art internal documents. [redacted]. Plaintiffs' NDA and internal documents reflect the thinking of individuals with inside knowledge of the invention, which the POSA would not have. For this reason, the Federal Circuit has held that the inventor's own non-prior-art regulatory communications, even where they characterize the prior art, are properly excluded from the obviousness analysis because those communications are "made through the lens of what the [inventors] invented." *Neptune Generics*, 921 F.3d at 1377. Plaintiffs' internal documents are similarly irrelevant here.

Teva also tries to assert, based on non-prior-art documents, [redacted]

[redacted]

* * *

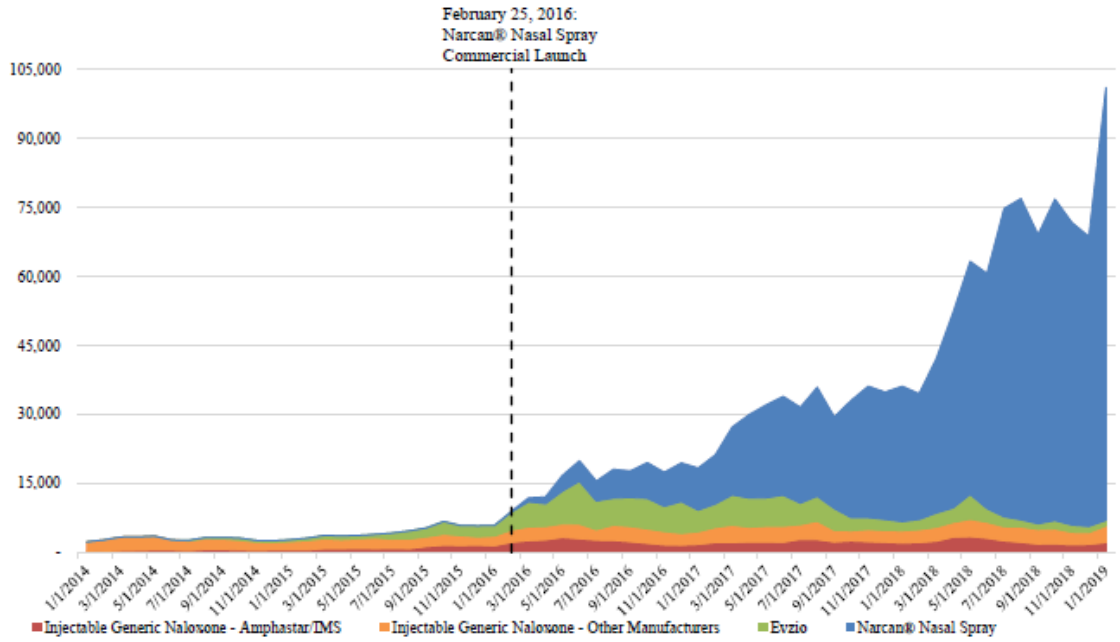
In short, Teva's obviousness case rests improperly on hindsight. Teva needs to go searching through the art, retrospectively combining bits and pieces from different prior art references, in order to identify the claimed elements, which even when they existed on their own had never been combined in the claimed manner. And it rests on hindsight because Teva—faced with the difficult reality that *no one, including Teva, foresaw the claimed invention*—resorts to Plaintiffs' own non-prior-art documents and reasoning in order to cobble together a supposed motivation to combine all of those elements. That is not how obviousness is properly analyzed.

### D. Objective Indicia of Nonobviousness Further Demonstrate That the Claimed Invention Would Not Have Been Obvious

On top of the serious flaws in Teva's *prima facie* case, the notion that the claims are obvious is undermined by objective indicia that the Court is required to consider to guard against hindsight. It is easy to contend, in retrospect, with knowledge of Plaintiffs' successful product, that the claimed invention is obvious. But the proper analysis must "avoid[] subconscious reliance on hindsight," and objective indicia are "powerful tools" for assessing obviousness without such hindsight bias. *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378 (Fed. Cir. 2012). The substantial objective evidence here strongly supports a finding of non-obviousness.

"Commercial success of an invention is significant evidence that the invention would not have been obvious and it should be given great weight." *Mitsubishi Chem. Corp. v. Barr Labs., Inc.,* 718

F. Supp. 2d 382, 436 (S.D.N.Y. 2010) (citing *Goodyear Tire & Rubber Co. v. Ray-O-Vac Co.*, 321 U.S. 275, 279 (1944)). NARCAN® Nasal Spray, the commercial embodiment of the claims, has been a tremendous success. [redacted] Although it launched only in the first quarter of 2016, *over 90% of* the prescriptions of naloxone in the retail market are now to NARCAN® Nasal Spray (as depicted below).




It is evident from these data that NARCAN® Nasal Spray satisfied a long-felt but unmet need for a needle-free community-use naloxone product, a need long recognized in the literature. This is further objective evidence of nonobviousness. *See Proctor & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009). NARCAN® Nasal Spray's swift rise to marketplace dominance despite the longstanding availability of other naloxone products—including the EVZIO® autoinjector that was also for community use—illustrates the tremendous unmet need that NARCAN® Nasal Spray satisfied. It is no surprise that NARCAN® Nasal Spray has been the subject of widespread praise, from state and local government bodies, first responder organizations, and companies in the medical industry, among others. This is also "probative and cogent evidence" of nonobviousness. *Institut Pasteur v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013).

Teva contends that there is no connection between this objective evidence and the merits of the claimed invention—known as "nexus." But there is a presumption of nexus where, as here, the objective evidence "is tied to a specific product and that product is the invention disclosed and claimed in the patent." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016). Teva does not dispute that NARCAN® Nasal Spray embodies all but two of the asserted claims. Instead, to overcome the presumption of nexus, Teva improperly attempts to disassemble the invention—a novel combination of device, formulation, and dose—and attribute NARCAN® Nasal Spray's marketplace dominance solely to elements (mostly the device) in the prior art. But consumers do not purchase only bits and pieces of NARCAN® Nasal Spray; the device alone would not treat opioid overdose without the right dose and formulation. Teva's "dissection" strategy contravenes common sense and binding precedent. *See, e.g.*, *WBIP*, 829 F.3d at 1330 ("[P]roof of nexus is not limited to only when objective evidence is tied to supposedly 'new' feature(s).").

In addition, as discussed above, numerous other groups were attempting to develop an intranasal formulation. Only Plaintiffs succeeded in bringing such a formulation to the U.S. market, and none of the other groups were successful in developing the claimed formulation. The law recognizes that such failures of others—including the failure to obtain FDA approval, which both Indivior and Amphastar experienced—is objective evidence of non-obviousness. *See, e.g.*, *In re Cyclobenzaprine Hydrochloride Extended-Release Patent Litig.*, 676 F.3d 1063, 1081–82 (Fed. Cir. 2012). [redacted] *See, e.g.*, *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000) (recognizing copying as objective evidence of non-obviousness). These real-world facts are flatly inconsistent with the litigation-driven notion that the asserted claims are obvious.

It is also significant that many in the field expressed skepticism regarding, for example, the claimed 4 mg dose of the invention before NARCAN® Nasal Spray launched. For example, [redacted]

[redacted] Expressions of skepticism with regard to the invention, [redacted], support a finding of nonobviousness. *Monarch Knitting Machinery v. Sulzer Morat GmbH*, 139 F.3d 877, 885 (Fed. Cir. 1998).

The claimed invention also has numerous unexpected properties, as compared with the closest prior art (Wyse), which support a finding of non-obviousness. *See, e.g.*, *Proctor & Gamble Co.*, 566 F.3d at 994. In addition to the unexpected stability of an intranasal naloxone formulation containing BZK and EDTA, the claimed invention also exhibits unexpectedly high pharmacokinetic parameters. For example, NARCAN® Nasal Spray exhibits a bioavailability that is a 56% improvement over Wyse's formulation.

## III. The Asserted Claims Are Not Invalid Under 35 U.S.C. § 112

As to some of the asserted claims, Defendants also argue that they do not satisfy § 112's written description requirement that the specification show that the inventor "had possession of" the invention. *Centrak, Inc. v. Sonitor Techs., Inc.*, 915 F.3d 1360, 1365 (Fed. Cir. 2019). "It is not necessary that the claimed subject matter be described identically"; rather, the specification "must convey to those skilled in the art that [the] applicant had invented the subject matter later claimed." *In re Wilder*, 736 F.2d 1516, 1520 (Fed. Cir. 1984).

Among the smattering of § 112 arguments, Teva argues that claims 3 and 34 of the '838 patent are invalid because they specify "about 0.1% (w/v) disodium edetate" along with particular amounts of other excipients. Teva complains that although the patent's specification describes the precise amounts of the other excipients, the 0.1% EDTA is only disclosed as an endpoint of a range of "between about 0.1 mg and about 0.5 mg of a stabilizing agent" in about 100 µL—*i.e.*, about 0.1% to about 0.5%. *See* '838 patent (Ex. YY) at 22:4–18. Meanwhile, the patent also provides that

"the stabilizing agent is disodium edetate." *Id.* at 22:31. This language clearly would have signified to the POSA that inventors had possessed the idea of formulations having 0.1% EDTA. Teva also argues that certain claims of the '838 patent lack written description support for the term "naloxone." This makes no sense, as the '838 patent expressly defines "naloxone" and describes various possible salt forms of naloxone. The inventors were plainly in possession of the idea of using "naloxone" in the claimed invention. And Teva tries to argue that the specification does not describe devices that "spray of 25–200 μL" even though it describes a number of devices capable of delivering such sprays, including "[m]etered spray pumps" that "have dominated the nasal drug delivery market since they were introduced" and "typically deliver 100 μL (25-200 μL) per spray." '177 patent (Ex. SS) at 11:18–20. Teva's other § 112 arguments are equally unpersuasive.

## CONCLUSION

For all of these reasons, judgment should be entered in favor of Plaintiffs.

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Respectfully submitted,

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**CERTIFICATE OF SERVICE**

I hereby certify that a true and correct copy of the foregoing PLAINTIFFS' TRIAL BRIEF was caused to be served this 19th day of July 2019 through the Court's CM/ECF systems and electronic mail upon the following:

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